FORM PTO-1390 (REV 5-93) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 223/051

U S APPLICATION NO. (If known, see 37 CFR 1.5): 08/737446

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/CA95/00287	12 May 1995	12 May 1994

TITLE OF INVENTION: TREATMENT OF DIABETES

APPLICANT(S) FOR DO/EO/US: AMYLIN PHARMACEUTICALS, INC.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1) .
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
08/737446	PCT/CA95/00287	09 May 1995	09 May 1994

89 Rec'd PCT/PTO 08 NOV 1996

17. [XX] The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO..... $ ~~880.00~~ 910.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... **$ 680.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).. **$ 750.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37CFR 1.445(a)(2)) paid to USPTO..... **$ 1,010.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... **$ 94.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 910	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed		Number Extra	Rate		
Total 19 Claims	19	-20 =	0	X **$22.00**	$ 0.00	
Independent Claims	6	-3 =	3	X **$78.00**	$ 240.00	
Multiple dependent claims(s) (if applicable)				+ **$250.00**	$ 260.00	
TOTAL OF ABOVE CALCULATIONS =					$ 1,540.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).					$ 770.00	-
SUBTOTAL =					$ 770.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				+	$	
TOTAL NATIONAL FEE =					$ 770.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +					$	
TOTAL FEES ENCLOSED =					$ 770.00	
					Amount to be: refunded	$
					charged	$

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. [XX] Please charge my Deposit Account No. 01-0535 in the amount of $ 770.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [XX] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-0535. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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32,219
REGISTRATION NUMBER

Form PTO-1390 (REV 5-93)

TREATMENT OF DIABETES

Field of the Invention

The present invention relates to methods and compositions for treatment of diabetes.

Background of the Invention

The recent findings of the Diabetes Control and Complications Trial (DCCT) carried out by the U.S. National Institute of Health have emphasised the importance of doing everything possible to normalise blood glucose levels in diabetics to avoid or delay micro-vascular damage. Intensified insulin therapy has been shown by the trial to improve glycaemic control but is accompanied by the risk of hypoglycaemia. This limits the degree of glycaemic control which can be safely attempted, so that true normalisation of blood glucose levels cannot be achieved with insulin therapy alone.

Glucagon-like peptide 1(7-36)amide or glucagon-like insulinotropic peptide (GLIP) is a gastrointestinal peptide which potentiates insulin release in response to glycaemia in normal humans.

Glucagon-like insulinotropic peptide has been suggested for use either alone or in conjunction with oral hypoglycaemic agents in Type II or non-insulin dependent diabetes (Gutniak et al., (1992), N.E.J.M. vol. 326, p. 1316; International Patent Application No. WO93/18786). These authors have noted a synergistic effect between the peptide and oral hypoglycaemic agents in Type II diabetics.

The present inventor has found, unexpectedly, that administration of glucagon-like insulinotropic peptide permits improved glycaemic control in subjects with insulin-requiring diabetes.

Summary of Invention

In accordance with one embodiment of the present invention, a method is provided for treating insulin-requiring diabetes in a mammal comprising administering to the mammal in a suitable regimen an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b).

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b)

is used for the preparation of a medicament for use in the treatment of insulin-requiring diabetes in a suitable regimen which additionally comprises treatment with insulin.

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b)

is used for the preparation of a medicament which also includes insulin for treatment of insulin-requiring diabetes.

In accordance with a further embodiment of the invention, a pharmaceutical composition is provided for the treatment of insulin-requiring diabetes comprising an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) and a pharmaceutically acceptable carrier.

In accordance with a further embodiment of the invention, a method is provided for treating Type I diabetes in a mammal comprising administering to the mammal an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b).

In accordance with a further embodiment of the invention, a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) is used for the preparation of a medicament for use in the treatment of Type I diabetes.

Summary of Drawings

Figure 1A shows blood levels of glucose, Figure 1B shows C-peptide, Figure 1D shows human pancreatic polypeptide (HPP), Figure 1D shows glucagon and Figure 1E shows gastrin in Type I diabetic subjects after Sustacal meal alone (O) or Sustacal meal with GLIP infusion (•).

Figure 2A shows blood levels of glucose and Figure 2B C-peptide in Type I diabetic subjects during glucose infusion alone (O) or along with IV GLIP(•).

Figure 3A shows blood levels of glucose (expressed as the change (Δ) from baseline values at time zero) and Figure 3B shows C-peptide (expressed as the change (Δ) from baseline values at time zero) in Type I diabetic subjects after Sustacal meal and saline infusion (O) or Sustacal meal with infusion of 0.75 pm GLIP/kg/min (▲).

Figure 4A shows blood levels of glucose, Figure 4B shows C-peptide, Figure 4C shows insulin and Figure 4D shows human pancreatic polypeptide (HPP) in normal subjects after Sustacal meal alone (O) or Sustacal meal immediately preceded by a subcutaneous injection of 100 μg GLIP (●).

Figure 5A shows blood levels of glucose, Figure 5B shows C-peptide, Figure 5C shows insulin and Figure 5D shows human pancreatic polypeptide (HPP) in Type I diabetic subjects after Sustacal meal alone (O) or Sustacal meal immediately preceded by a subcutaneous injection of 100 μg GLIP (●).

Figure 6A shows blood levels of glucose, Figure 6B shows C-peptide, Figure 6C shows insulin, Figure 6D shows human pancreatic polypeptide (HPP), Figure 6E shows GLIP (GLIP-1) and Figure 6F gastrin in a Type I diabetic subject who received 5 Units regular human insulin and 50 μg GLIP subcutaneously prior to a Sustacal meal.

Detailed Description of the Invention

The glucagon-like peptide 1 fragments, glucagon-like peptide 1(7-36)amide and glucagon-like peptide 1(7-37), show essentially similar insulinotropic and other biochemical effects in humans and other mammals.

Glucagon-like peptide 1(7-36)amide is referred to herein as GLIP.

The present invention provides a method of treating Type I diabetes by administration of an effective amount of GLIP, or other glucagon-like peptide 1-related peptide, either alone or in conjunction with a regimen of insulin administration.

Although the discussion herein refers to use of "GLIP", it will be understood by those skilled in the art that the therapeutic methods of the invention may be practised by employing GLIP, glucagon-like peptide 1(7-37), an effective peptide including GLIP or glucagon-like peptide 1(7-37), or an effective fragment or analogue of GLIP or glucagon-like peptide 1(7-37).

As is seen in Figure 2, IV administration of GLIP along with intravenous glucose stimulated secretion of endogenous insulin in the subjects studied and gave improved control of blood glucose level. These subjects were in the remission phase, or so-called "honeymoon phase", of IDDM characterised by substantial remaining endogenous insulin secretion.

The same dose of GLIP (1.2 pm/kg/min) gave excellent control of blood glucose level in these subjects after a meal, as seen in Figure 1, Panel A. Under these conditions, GLIP infusion also prevented a significant increase in blood levels of C-peptide.

After the Sustacal meal, the test subjects showed normal secretion of pancreatic polypeptide (PP) but this response was absent during GLIP infusion (Figure 1, Panel C). It is believed that this abrogation of PP response was due to the delayed passage of the meal from the stomach to the small intestine as a result of GLIP administration. That it was not due to a general suppression of gastrointestinal peptide secretion is indicated by the normal gastrin response to the presence of food in the stomach in these subjects (Figure 1, Panel E).

Administration of GLIP prevented the mean rise in plasma glucagon levels stimulated by the meal in the absence of GLIP. Gastrin levels were not significantly affected.

Administration of a lower dose of GLIP (0.75 pmol/kg/min) along with a meal resulted in some increase in blood glucose and C-peptide, as seen in Figure 3. Although the increase in glucose was less than in the control experiment, the rise in C-peptide was similar to the control experiment.

GLIP is known to cause delay of gastric emptying in humans and other mammals (Wettergren et al., (1993), Digestive Diseases and Sciences, v. 38, p. 665). As seen in Figure 4, when GLIP is given subcutaneously to normal

subjects prior to ingestion of a meal, there is a delay of 30 to 60 minutes in the rise in blood glucose level. This delay is likely due to inhibition of gastric emptying.

When Type I diabetics were given GLIP subcutaneously prior to ingestion of a test meal, a lowering of blood glucose levels was seen compared to the control figures when no GLIP was administered (Figure 5, Panel A). The delayed rise in pancreatic polypeptide (HPP) levels (Panel D) indicate delayed gastric emptying. As seen from Panels B and C, there was no enhancement of insulin secretion over control levels to account for the lower glucose levels.

It may be that the improved glycaemic control seen with GLIP administration in Type I diabetics is due to delay of the post-meal rise in blood glucose through the interval required for the establishment of the effect of insulin.

The efficacy of GLIP administration along with insulin in restraining the expected rise in blood glucose after a standard meal in Type I diabetes is seen in Example 6 and Figure 6. 50 μg GLIP was administered along with half the insulin dose that would usually be required to deal with the test meal. As seen in Figure 6, Panel A, blood glucose did not rise above 8 mM. With this size of meal and half the usual insulin dose, considerably higher blood glucose levels would have been expected, in the absence of the effect of GLIP. For example, with this meal and no insulin, blood glucose levels reached 15 mM, as seen in Figure 5, Panel A.

As seen from Figure 6, Panel E, GLIP was cleared from the blood in about two hours so that pre-meal GLIP administration would not be expected to interfere with management of subsequent meals.

When GLIP is used to improve glycaemic control in Type I diabetics having residual endogenous insulin secretion capacity, both the insulinotropic effect of the

hormone and its effect to delay gastric emptying will contribute to its effect. Some remission phase Type I subjects may be sufficiently controlled by administration of GLIP alone, without exogenous insulin.

In the majority of patients with Type I diabetes, however, treatment with a regimen including both GLIP and insulin is likely to be required. These studies indicate that the observed effects of GLIP on glycaemia are not dependent on stimulation of insulin release and are therefore not limited to diabetics retaining residual insulin secreting capacity.

The use of GLIP in treating Type I diabetes, in accordance with the present invention, provides improved glycaemic control and reduces post-prandial excursions of blood glucose. This accords with the current emphasis on normalising blood glucose levels as much as possible, to reduce diabetic complications.

Furthermore, a regimen combining administration of insulin and administration of GLIP, in accordance with the present invention, is applicable to patients with insulin requiring diabetes which would not strictly be classified as Type I.

An insulin-requiring diabetic is a diabetic who is unable to avoid hyperglycaemia without the use of insulin. The invention further provides a method for treating patients with diabetes which is etiologically Type II but requires insulin treatment.

Diabetics frequently find the requirements for food intake and insulin administration at midday particularly irksome and an interference with work and other activities. By administering GLIP to diabetic subjects at breakfast time, along with administration of longer acting insulin if necessary, diabetics may be able to omit lunch or greatly reduce the size of that meal, and thereby avoid the need for midday insulin.

The delayed adsorption of nutrients when both GLIP and insulin are administered before breakfast will also reduce the risk of hypoglycaemia if lunch is delayed.

The studies described herein also indicate that a therapeutic regimen including both GLIP and insulin will in many cases permit the use of reduced doses of insulin. This is also beneficial in the avoidance of hypoglycaemia.

GLIP or its related peptides which may be employed in the treatment methods described herein may be administered orally, nasally or parenterally. Parenteral administration may be by a variety of routes including subcutaneous or intravenous infusion, and subcutaneous or intravenous injection.

The regimen of GLIP or GLIP and insulin administration required to give the desired glycaemic control in a diabetic patient can be readily determined by those skilled in the management of diabetic patients.

As will be understood by those skilled in the art, any suitable insulin preparation may be used in conjunction with GLIP administration in the combined regimen described herein.

Suitable insulins include regular or fast-acting insulin to maintain blood glucose control through the post-prandial interval, with or without addition of longer-acting insulin to maintain blood glucose control through the post-absorptive interval.

The dosages of GLIP required may be optimised for each subject by evaluation of the degree of glycaemic control achieved by trial doses.

Another convenient method of monitoring the level of effect of GLIP on a subject is to monitor the blood level of pancreatic polypeptide in response to trial doses of GLIP.

Such dosage and regimen adjustments are now commonplace, for example for diabetics treated with mixtures of fast and slow acting insulins. These mixed

preparations are available in various ratios of fast to slow and an appropriate ratio must be selected for a particular patient by trial doses. One patient may even employ insulin preparations of different ratios to handle varying sizes of meals. By similar testing, a suitable GLIP and insulin regimen may be selected.

GLIP and insulin may be administered separately or may be prepared and administered as a single formulation.

EXAMPLES

Example 1

7 subjects with remission phase Type I diabetes were studied after ingestion of a standardised meal of Sustacal (Upjohn) (delivering 30 kg/kg). Subjects continued their normal insulin treatment programme on the day prior to the test and, on the day of the test, omitted their morning insulin injection and arrived fasting at 8:00 am. On one test day they were given the Sustacal meal, followed immediately by initiation of intravenous infusion of GLIP (synthetic human GLIP-(7-36)amide from Peninsula, U.K.) at an infusion rate of 1.2 pm/kg/min. Infusion was continued for 120 minutes. Blood levels of glucose, C-peptide, gastrin, glucagon and HPP were monitored by standard radioimmunoassay methods in samples taken before and at intervals during the study, up to 180 minutes. On another test day, subjects were given the Sustacal meal alone and the same analytes were similarly monitored.

Results are shown in Figure 1.

Example 2

Four subjects with remission phase Type I diabetes were studied during intravenous glucose infusion. Subjects prepared for the tests as described in Example 1, but received an intravenous infusion of glucose (20 g

over 60 min. constant rate) instead of the Sustacal meal. On one test day, they also received intravenous GLIP for 60 minutes (1.2 pm/kg/min for 60 min.) and on another test day, they received IV glucose alone. Blood levels of glucose and C-peptide were monitored as in Example 1.

The results are shown in Figure 2.

Example 3

Four subjects with remission phase Type I diabetes were studied during infusion with 0.75 pm/kg/min GLIP for 120 minutes after a Sustacal meal.

The test was conducted as described in Example 1 and blood glucose and C-peptide levels were measured. On a further test day, the subjects were studied during saline infusion after a similar Sustacal meal.

Results are shown in Figure 3.

Example 4

7 normal volunteers were studied after ingestion of a Sustacal meal either alone or immediately preceded by a subcutaneous injection of 100 μg GLIP.

Results are shown in Figure 4. *indicates statistically significant differences between treatments ($p<0.05$).

A delay in increase in blood levels of glucose, HPP, C-peptide and insulin was seen. When the experiment was repeated with 50 μg or 200 μg dose of GLIP, proportionally shorter and longer delays, respectively, were seen.

Example 5

7 Type I diabetic subjects were studied. Subjects omitted their morning insulin injection on the days of the tests and were given a Sustacal meal alone one day and, on another day, a Sustacal meal immediately preceded by a subcutaneous injection of 100 μg GLIP.

The results are shown in Figure 5. *indicates statistically significant differences between treatments ($p<0.05$).

Example 6

One Type 1 diabetic subject was given GLIP along with insulin and the effects on post-prandial glycaemia observed. The subject received 5 units of insulin and 50 μg GLIP as subcutaneous injections immediately prior to ingestion of a Sustacal meal as described in Example 1. The results are shown in Figure 6. Blood levels of GLIP were monitored by a standard radioimmunoassay method.

Although only preferred embodiments of the present invention have been described, the present invention is not limited to the features of these embodiments, but includes all variations and modifications within the scope of the claims.

I CLAIM:

1. A method of treating insulin-requiring diabetes in a mammal comprising administering to the mammal in a suitable regimen an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b).

2. The method of claim 1 wherein the mammal is a human.

3. The method of claim 2 wherein an effective amount of insulin and an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) are administered to the human at a selected time prior to ingestion of a meal.

4. The method of any of claims 1 to 3 wherein the insulin-requiring diabetes is Type I diabetes.

5. The method of any of claims 1 to 3 wherein the insulin-requiring diabetes is Type II diabetes.

6. Use of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) for the preparation of a medicament for use in the treatment of insulin-requiring diabetes in a suitable

regimen which additionally comprises treatment with insulin.

7. Use of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) for the preparation of a medicament which also includes insulin for treatment of insulin-requiring diabetes.

8. Use of a peptide in accordance with claim 6 or 7 wherein the insulin-requiring diabetes is Type I diabetes.

9. Use of a peptide in accordance with claim 6 or 7 wherein the insulin-requiring diabetes is Type II diabetes.

10. A pharmaceutical composition for the treatment of insulin-requiring diabetes comprising an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b) and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition in accordance with claim 10 for the treatment of Type I diabetes.

12. The pharmaceutical composition of claim 10 or 11 further comprising an effective amount of insulin.

13. A method of treating Type I diabetes in a mammal comprising administering to the mammal an effective amount of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b).

14. Use of a peptide comprising a peptide selected from the group consisting of

(a) glucagon-like peptide 1(7-37);

(b) glucagon-like peptide 1(7-36)amide; and

(c) an effective fragment or analogue of (a) or (b)

for the preparation of a medicament for use in the treatment of Type I diabetes.

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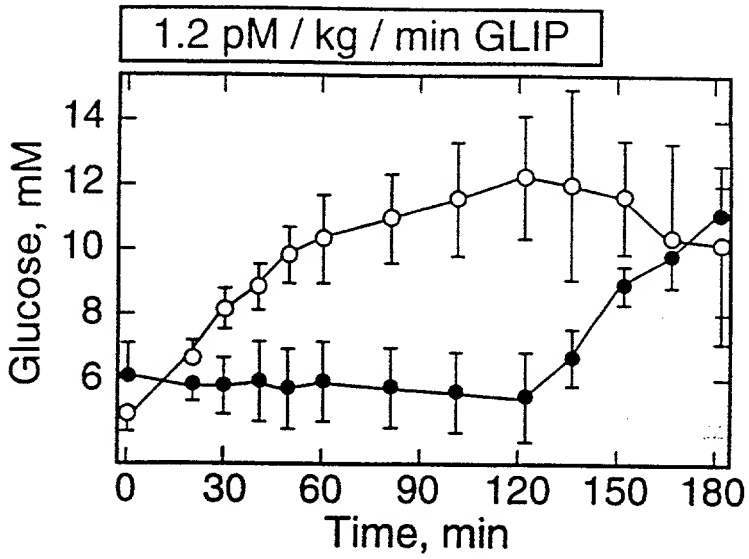

FIG.1A.

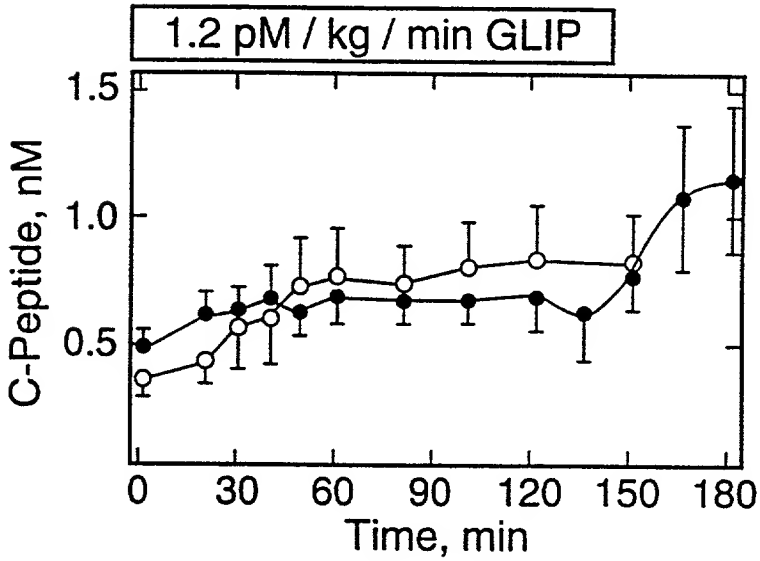

FIG.1B.

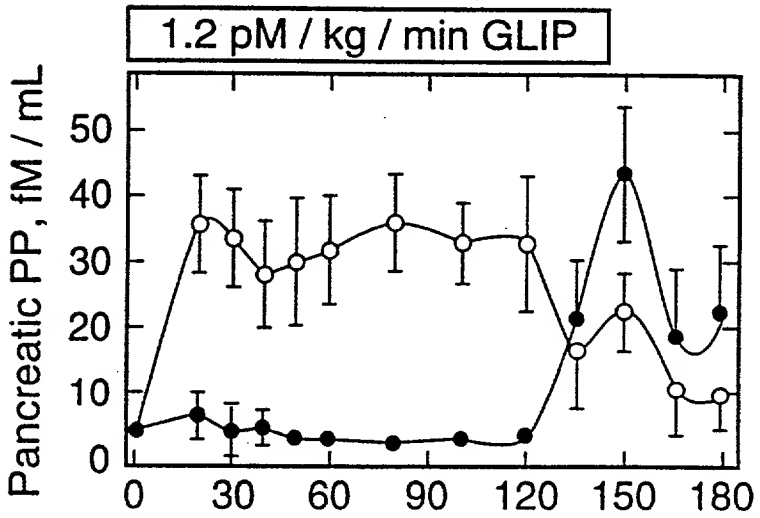

FIG.1C.

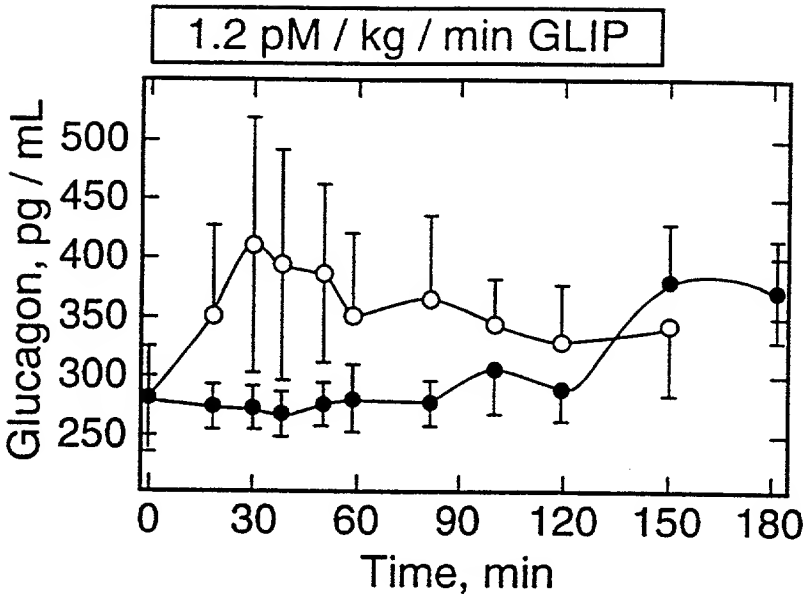

FIG.1D.

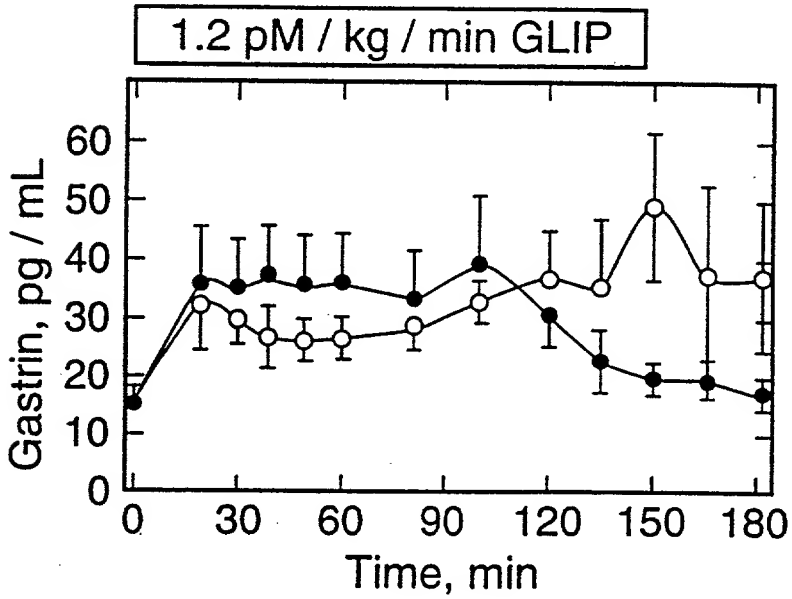

FIG.1E.

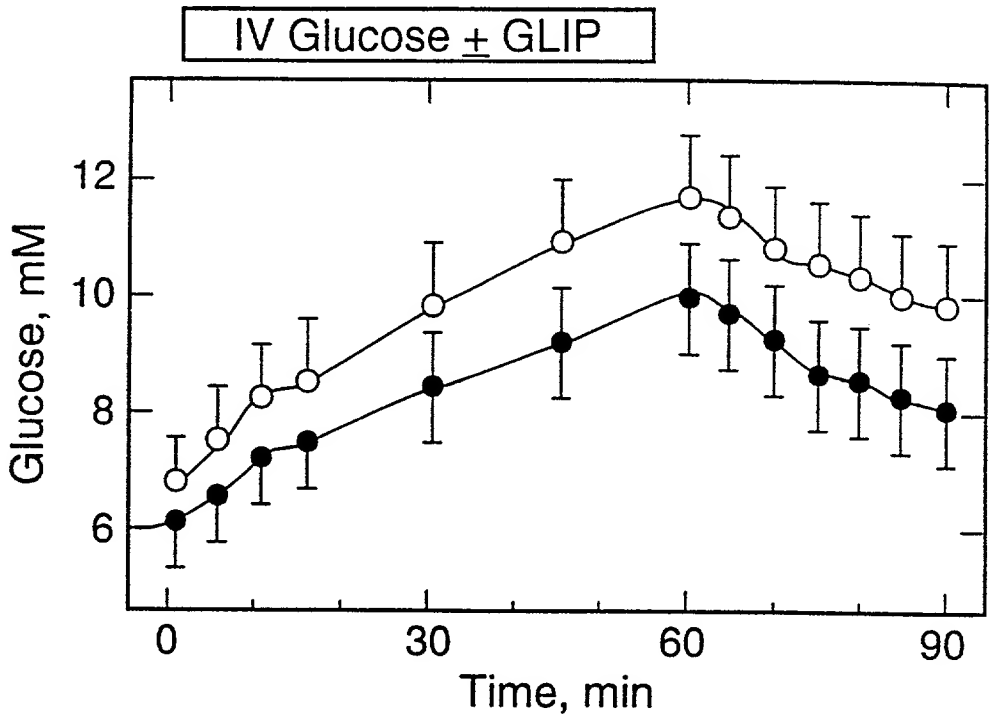

FIG.2A.

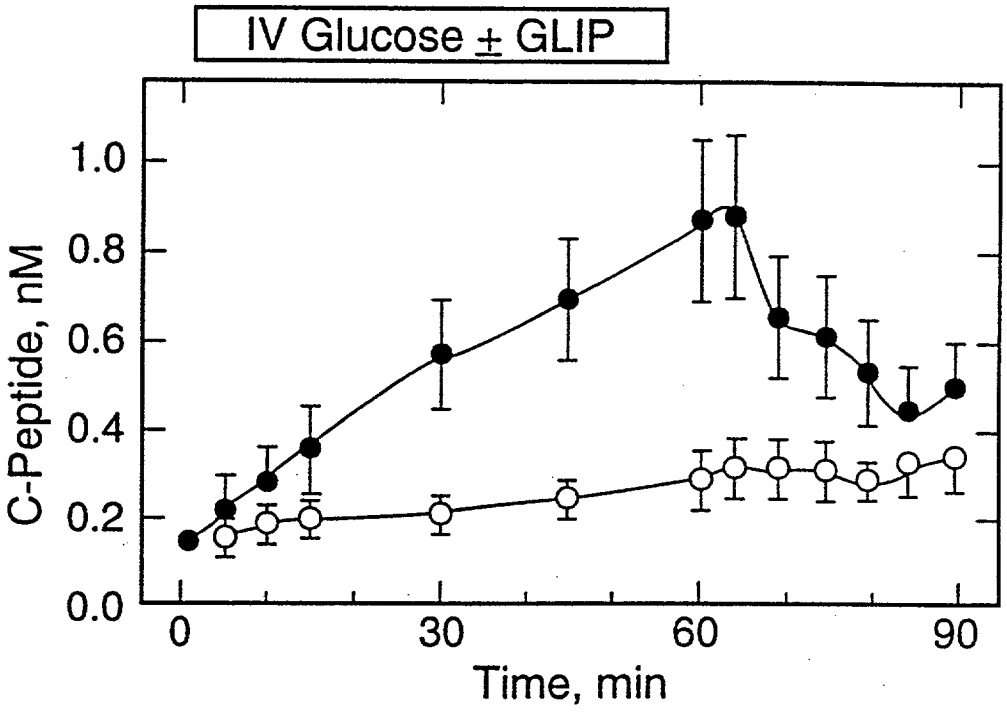

FIG.2B.

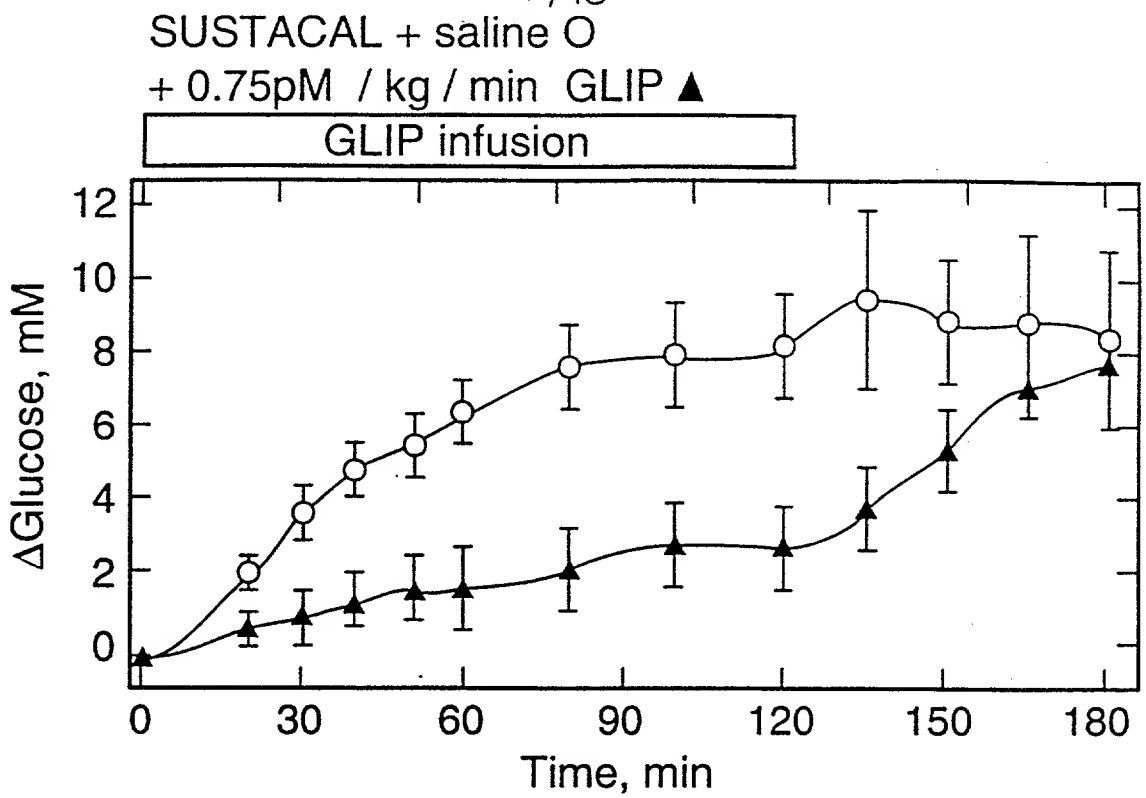

FIG. 3 A.

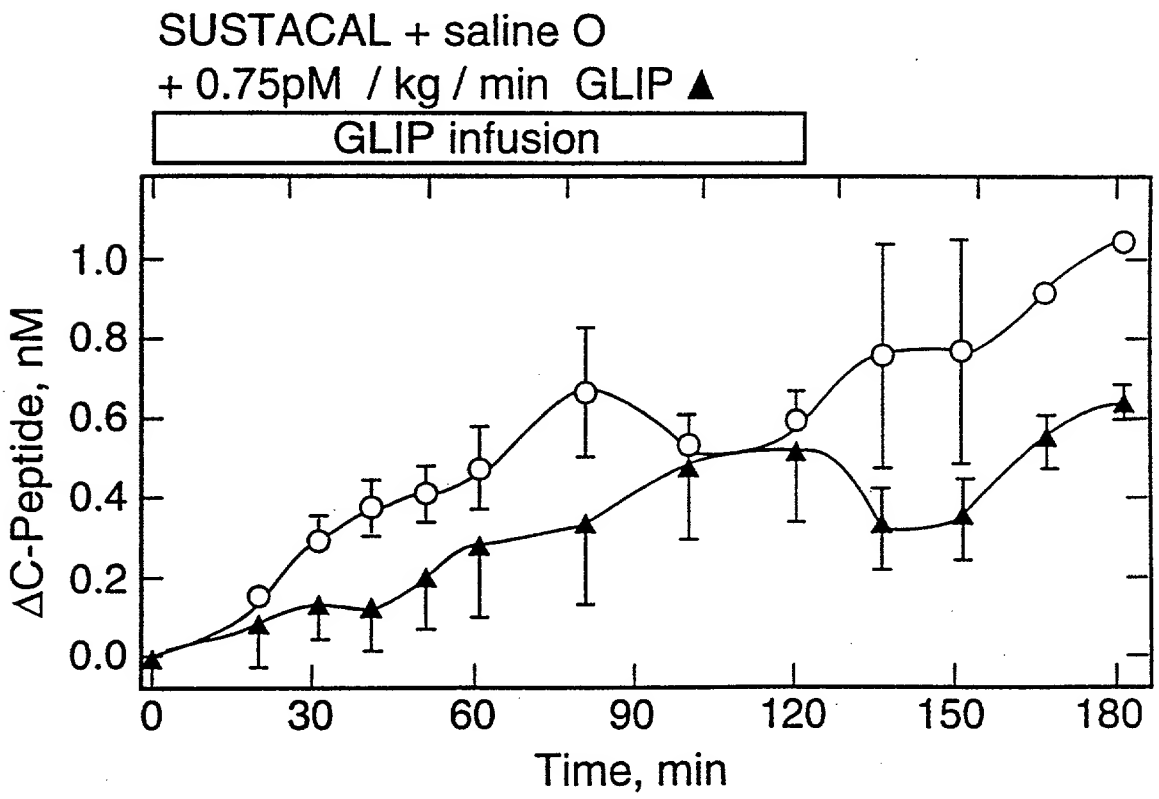

FIG. 3B.

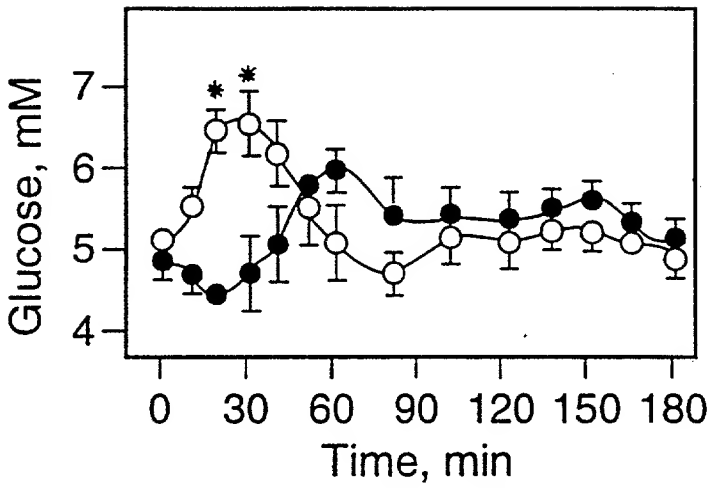

FIG.4A.

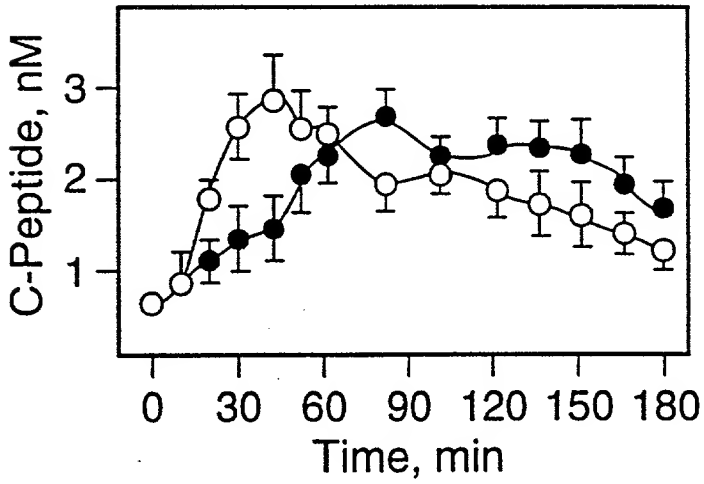

FIG.4B.

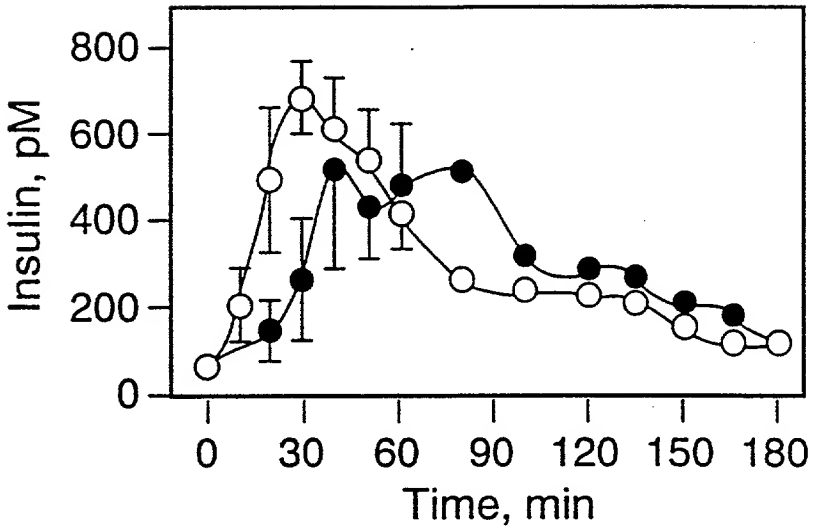

FIG.4C.

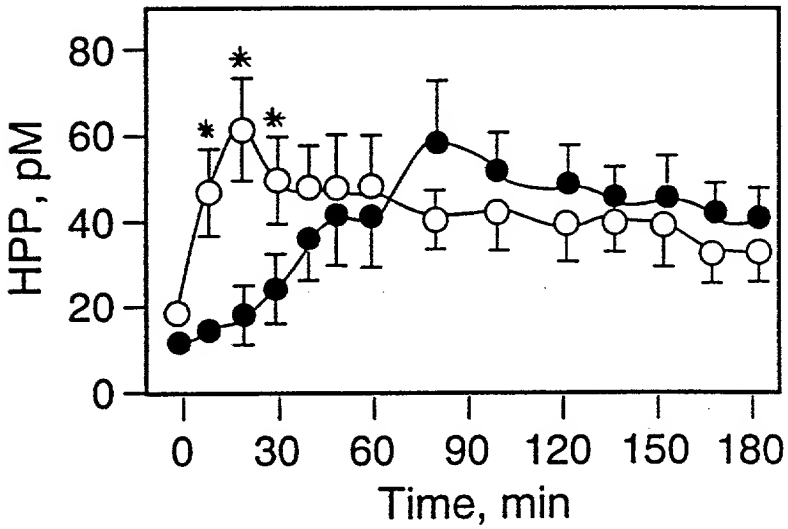

FIG.4D.

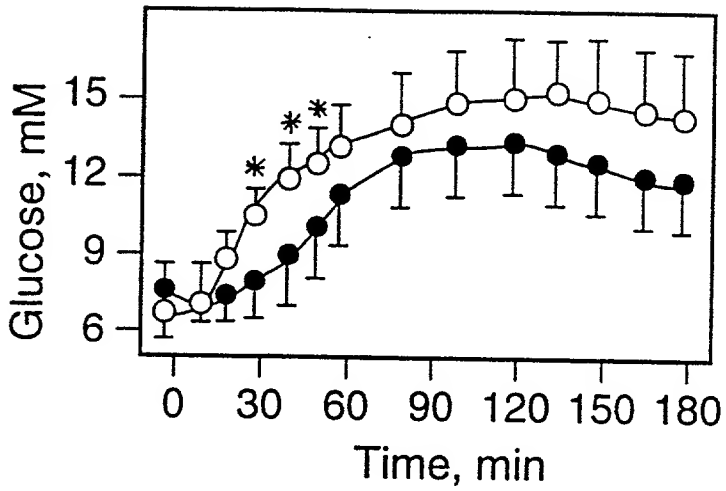

FIG.5A.

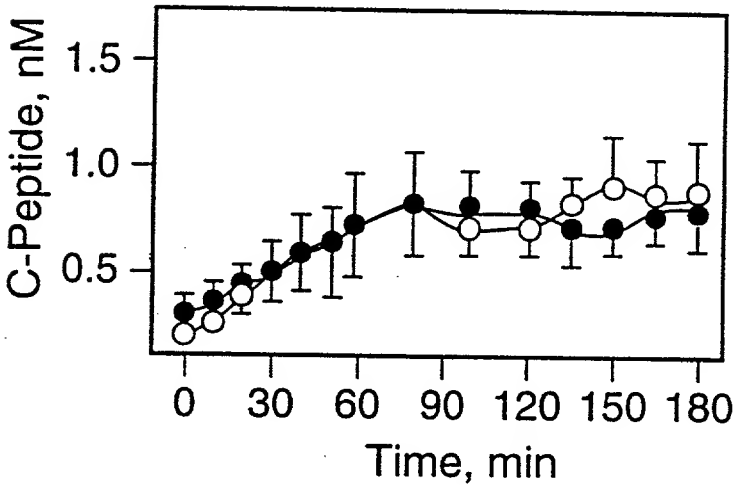

FIG.5B.

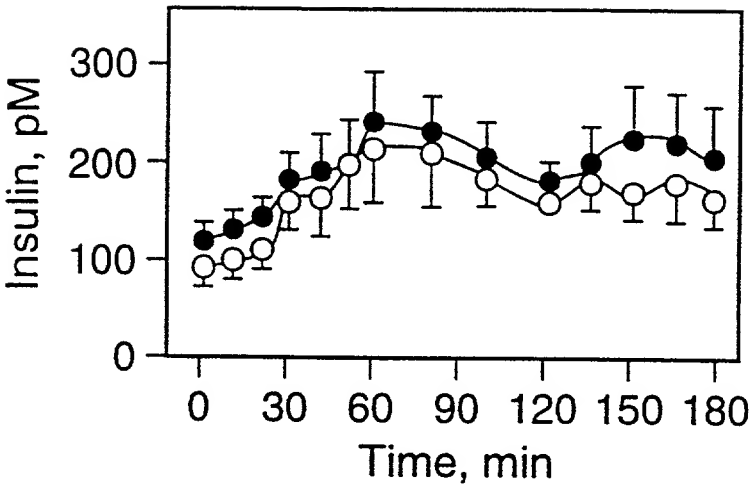

FIG.5C.

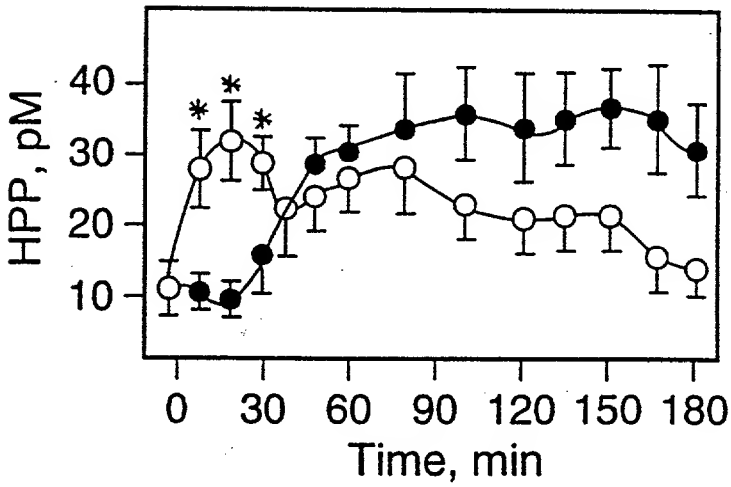

FIG.5D.

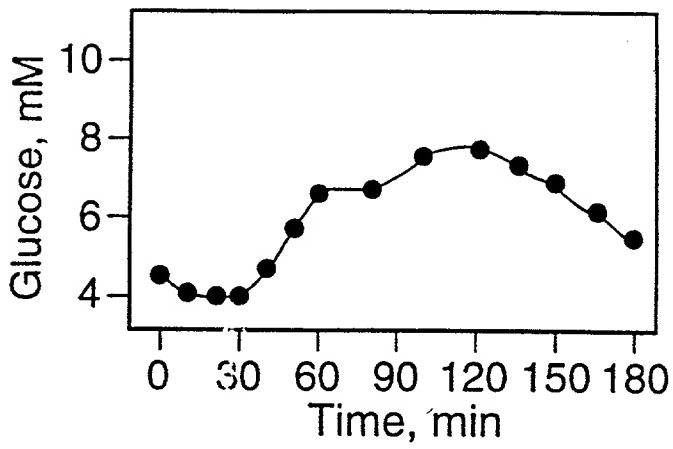

FIG.6A.

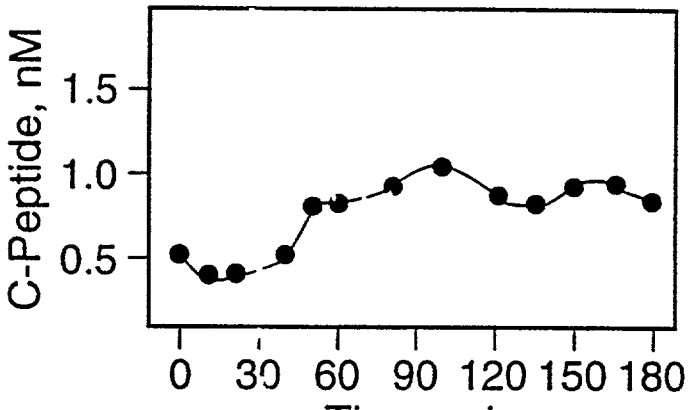

FIG.6B.

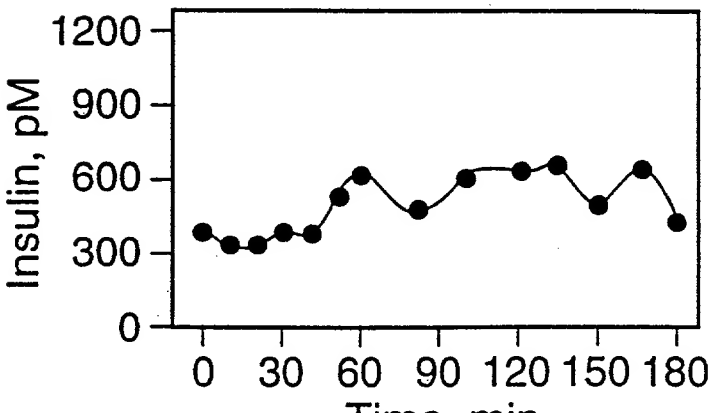

FIG.6C.

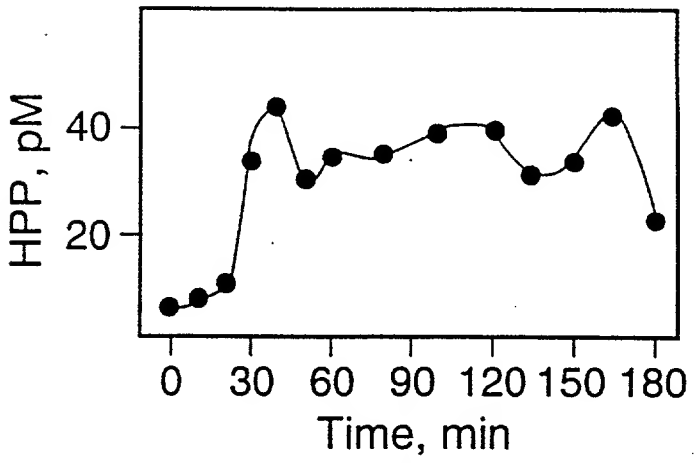

FIG.6D.

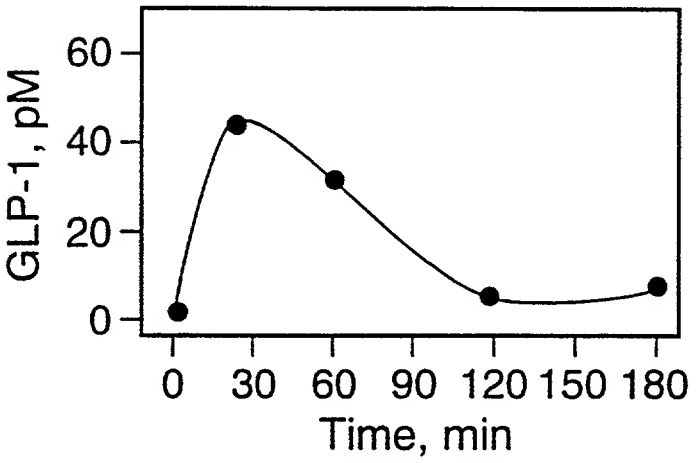

FIG.6E.

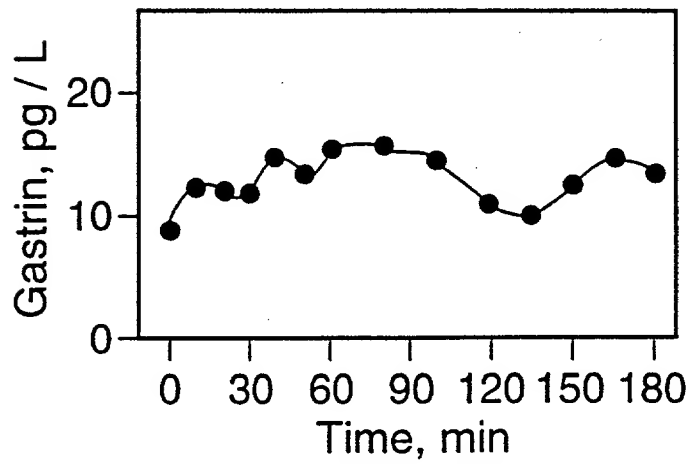

FIG.6F.

PATENT
Attorney Docket No. 223/051

Applicant or Patentee: AMYLIN PHARMACEUTICALS, INC.
Serial or Patent No.: PCT/CA95/00287
Filed or Issued: MAY 12, 1995
For: TREATMENT OF DIABETES

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 C.F.R.1.9(f) and 1.27(c)) - SMALL BUSINESS CONCERN

I hereby declare that I am:

_____ the owner of the small business concern identified below:
__X__ an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN: AMYLIN PHARMACEUTICALS, INC.
ADDRESS OF CONCERN: 9373 TOWNE CENTRE DRIVE
SAN DIEGO, CALIFORNIA 92121

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 C.F.R. 121.3-18, and reproduced in 37 C.F.R. 1.9(d), for purposes of paying reduced fees under Section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of it affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full--time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third-party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the above-entitled invention described in

__X__ the specification filed herewith
____ application serial number _____, filed __
_____ Patent No. _____, issued _____

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 C.F.R. 1.9(d) or by any concern which would not qualify as a small business concern under 37 C.F.R. 1.9(d) or a nonprofit organization under 37 C.F.R. 1.9(e).

NAME _____
ADDRESS _____
_____
_____

____ INDIVIDUAL ____ SMALL BUSINESS CONCERN ____ NONPROFIT ORGANIZATION

NAME _____
ADDRESS _____
_____
_____

____ INDIVIDUAL ____ SMALL BUSINESS CONCERN ____ NONPROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to

paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small business entity is no longer appropriate. (37 C.F.R. 1.28(b)).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so mad are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING:	Bradford J. Duft
TITLE OF PERSON OTHER THAN OWNER:	Vice President and General Counsel
ADDRESS OF PERSON SIGNING:	9373 Towne Centre Drive San Diego, California 92121

Signature _____ Date 8 Nov 96

937, 446 #3

Attorney's Docket No. 223/051

IN THE UNITED STATES

☐ **RECEIVING OFFICE (RO/US)**
☒ **DESIGNATED OFFICE (DO/US)**
☐ **ELECTED OFFICE (EO/US)**

PCT/CA95/00287	05/12/95	05/12/94
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

TREATMENT OF DIABETES
TITLE OF INVENTION

DUPRE, John
APPLICANT(S)

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

VERIFIED CERTIFICATION OF EXPRESS MAILING DATE (INTERNATIONAL APPLICATION (37 CFR 1.10(c))

I declare that, on 1/10/97, I deposited, with the United States Postal Service, in an envelope "Express Mail, Post Office to Addressee," bearing Label Number RB921444147, addressed to the "Assistant Commissioner for Patents, Washington, D.C. 20231," and having an express mail certification that I executed, the following papers:

Copy of form PCT/DO/EO/905, executed Declaration, and return reply postcard

A copy of these papers from the file of this application is attached.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Cynthia N. McGarvie

(typed or printed name of person making this verified statement)

Date 1/10/97

Signature of person making this verified statement

Verified Certification of Express Mailing Date (International Application) [13-12])—page 2 of 2)

Combined Declaration For Patent Application and Power of Attorney (Continued) | ATTORNEY'S DOCKET NUMBER 223/051

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (IF ANY)		
PCT/CA95/00287	12 May 1995			XX

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

Bradford J. Duft, Reg. No. 32,219

Send Correspondence to:	Direct Telephone Calls to: (name and telephone number)
Bradford J. Duft Lyon & Lyon LLP 633 West Fifth Street, Los Angeles CA 90071	213-489-1600

201	FULL NAME OF INVENTOR	FAMILY NAME DUPRE	FIRST GIVEN NAME John	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY London (HX	STATE OR FOREIGN COUNTRY Ontario, Canada	COUNTRY OF CITIZENSHIP Canadian
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 72 Sherwood Ave	CITY London, Ontario	STATE & ZIP CODE/COUNTRY Canada N6A 262
202	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
203	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
John Dupre		
DATE Jan 8 1997	DATE	DATE

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(Combined Declaration For Patent Application and Power of Attorney—PTO 1391 [13-11]—page 2 of 2)

U.S. Patent and Trademark Office FORM 13-11 13-116.5

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(Includes Reference to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: 223/051

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TREATMENT OF DIABETES

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Serial No. _____

on _____.

and was amended

on _____ (if applicable).

☒ was filed as PCT international application

Number PCT/CA95/00287

on 12 May 1995.

and was amended under PCT Article 19

on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (IF PCT, INDICATE "PCT")	APPLICATION NUMBER	DATE OF FILING (DAY, MONTH, YEAR)	PRIORITY CLAIMED UNDER 35 USC 119
GB	940946.8	12.05.94	☒ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO
			☐ YES ☐ NO

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(Combined Declaration For Patent Application and Power of Attorney—PTO 1391 [13-11]—page 1 of 2)